804. *Carcinogenic Nitrogen Compounds. Part XII.* Fluorine-containing 1 : 2- and 3 : 4-Benzacridines.*

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Four fluorine-containing 5-methyl-1 : 2- and -3 : 4-benzacridines have been synthesised by the modified Bernthsen reaction, for biological examination as potential carcinogenic agents. Several other new fluorinated compounds have also been prepared.

The biological effect of introducing halogen into carcinogenic hydrocarbons and related compounds has rarely been investigated. Some chlorine-containing derivatives of 1 : 2-benzanthracene (Newman, *J. Amer. Chem. Soc.*, 1938, **60**, 1368; Newman and Orchin, *ibid.*, p. 586; 1939, **61**, 244; Shear and Leiter, *J. Nat. Cancer Inst.*, 1940, **1**, 303; Lacassagne *et al.*, *Compt. rend.*, 1948, **227**, 1119), of the two angular benzacridines (Buu-Hoï, *J.*, 1950, 1146), and in the carbazole series (Buu-Hoï *et al.*, *J. Org. Chem.*, 1951, **16**, 309, 1198; *J.*, 1952, 279) have been investigated; however, no fluorinated molecules in these series have been prepared. Such compounds are of interest, because the physical and chemical properties of the fluorine substituent are closer to those of hydrogen. This finds biological expression in the ability of 4-amino-2-fluorobenzoic acid to antagonise the bacteriostatic activity of sulphanilamide (cf. Sexton, " Chemical Constitution and Biological Activity," Spon, London, 1949, p. 119) and in the antagonistic properties of 3-fluorotyrosine and 3-fluorophenylalanine towards phenylalanine in certain bacteria (Mitchell and Niemann, *J. Amer. Chem. Soc.*, 1947, **60**, 1232).

Synthesis of four fluoro-1 : 2- and -3 : 4-benzacridines is now reported, all bearing a methyl group in 5-position in view of the known favourable effect of *meso*-substitution

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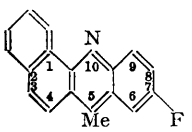
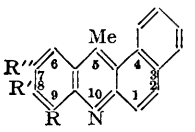
on carcinogenic activity in this series (cf. Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22; Buu-Hoï and Zajdela, *Acta Unio Intern. contra Cancrum*, 1950, **7**, 184). Condensation of *p*-fluoroaniline with α- and β-naphthol in the presence of iodine was found easily to yield *N*-*p*-fluorophenyl-α- and *N*-*p*-fluorophenyl-β-naphthylamine, whereas in the case of *p*-chloroaniline, similar condensations resulted in partial or complete loss of the halogen (Knoevenagel, *J. pr. Chem.*, 1914, **89**, 17); the modified Bernthsen reaction of these secondary arylamines with acetic anhydride (cf. Buu-Hoï and

(I) 

 (II)

Lecocq, *Compt. rend.*, 1944, **218**, 792) gave respectively 7-fluoro-5-methyl-1 : 2- (I) and 7-fluoro-5-methyl-3 : 4-benzacridine (II; R = R′ = H, R″ = F). *o*-Fluoroaniline also underwent condensation with β-naphthol without loss of fluorine, to give *N*-*o*-fluorophenyl-β-naphthylamine, Bernthsen reaction then yielding 9-fluoro-5-methyl-3 : 4-benzacridine (II; R = F, R′ = R″ = H). 7-Fluoro-5 : 8-dimethyl-3 : 4-benzacridine (II; R = H, R′ = Me, R″ = F) was similarly prepared *via* *N*-(4-fluoro-3-methylphenyl)-β-naphthylamine, from 4-fluoro-3-methylaniline. The last-mentioned benzacridine is assigned the 7-fluoro-5 : 8-dimethyl structure in view of the *para*-directing influence of methyl in acridine syntheses, but the alternative 7-fluoro-5 : 8-dimethyl orientation is not excluded. 4-Fluoro-3-methylaniline was synthesised from *o*-fluorotoluene by Friedel–Crafts acetylation, and Beckmann rearrangement of the oxime of the resulting 4-fluoro-3-methylacetophenone; orientation of the entrant acyl radical was inferred from Schiemann's observations (*Ber.*, 1929, **62**, 1797) that, in nitration, the directing effect of the fluorine atom superseded that of the methyl group (cf. the acetylation of *o*-chlorotoluene; Claus, *J. pr. Chem.*, 1891, **43**, 356; 1892, **46**, 26). A more rigid proof of the constitution of our ketone was obtained by its hypobromite oxidation to a fluorotoluic acid which must be 4-fluoro-3-methylbenzoic acid, as it was different from the known 3-fluoro-4-methylbenzoic acid (Paterno and Oliveri, *Gazzetta*, 1882, **12**, 93).

The benzacridines described herein are undergoing biological examination for carcinogenic activity by Professor Lacassagne and Dr. Zajdela, and have shown considerable toxicity.

Experimental

N-p- *and* -o-*Fluorophenyl-α-naphthylamine.*—*p*-Fluoroaniline (10 g.; prepared by reduction of *p*-fluoronitrobenzene), α-naphthol (18 g.), and iodine (0·2 g.) were gently refluxed for 12 hours; the cooled product was taken up in benzene, washed with aqueous sodium hydroxide and with water, dried (Na_2SO_4), freed from solvent, and distilled. N-p-*Fluorophenyl-α-naphthylamine* (11 g.) had b. p. 275—278°/25 mm., and crystallised from methanol as fine colourless prisms, m. p. 91° (Found: C, 80·8; H, 5·1. $C_{16}H_{12}NF$ requires C, 81·0; H, 5·0%). A similar reaction performed with *o*-fluoroaniline (prepared by reduction of *o*-fluoronitrobenzene) gave N-o-*fluorophenyl-α-naphthylamine* (8 g.), forming from methanol silky colourless needles, m. p. 90° (Found: C, 80·7; H, 5·2%).

7-*Fluoro-5-methyl*-1 : 2-*benzacridine.*—*N*-*p*-Fluorophenyl-α-naphthylamine (6 g.), freshly fused zinc chloride (6 g.), and acetic anhydride (6 g.) were heated at 180—185° for 18 hours; after cooling, the mixture was treated with aqueous sodium hydroxide, the insoluble part taken up in toluene, and the toluene solution dried (Na_2SO_4). After removal of the solvent, the residue gave on vacuum-distillation (b. p. >290°/20 mm.) 7-*fluoro-5-methyl*-1 : 2-*benzacridine*, crystallising from ethanol as silky pale yellow needles (3 g.), m. p. 166°, giving an intense greenish-yellow colour with sulphuric acid (Found: C, 82·7; H, 4·5. $C_{18}H_{12}NF$ requires C, 82·8; H, 4·6%). The corresponding *picrate* formed from benzene deep yellow prisms, m. p. 217—218° (decomp. above 200°) (Found: N, 11·2. $C_{24}H_{15}O_7N_4$ requires N, 11·4%).

7-*Fluoro-5-methyl*-3 : 4-*benzacridine.*—Similarly prepared from *N*-*p*-fluorophenyl-β-naphthylamine (Smith, *J. Org. Chem.*, 1951, **16**, 415), this derivative formed from ethanol pale yellow

needles (5 g.), m. p. 177° (Found : C, 82·8; H, 4·8%); its picrate formed from toluene orange-yellow prisms, decomp. above 210°.

N-o-*Fluorophenyl*-β-*naphthylamine*.—*o*-Fluoroaniline (10 g.), β-naphthol (10 g.), and iodine (0·2 g.) were refluxed for 8 hours, and worked up in the usual way; the secondary amine obtained (15 g.; b. p. 251—253°/16 mm.) crystallised from methanol as colourless needles, m. p. 82° (Found : C, 81·1; H, 5·2%).

9-*Fluoro*-5-*methyl*-3 : 4-*benzacridine*.—This *fluoro*-compound formed from ethanol fine yellowish needles, m. p. 170—171° (Found : C, 82·7; H, 4·8%); its picrate crystallised from benzene as deep yellow prisms, decomp. above 200°.

4-*Fluoro*-3-*methylacetophenone*.—A solution of *o*-fluorotoluene (30 g.) and acetyl chloride (22 g.) in dry carbon disulphide (150 c.c.) was treated with powdered aluminium chloride (46 g.), and the mixture obtained kept at room temperature for 24 hours and then refluxed for 2 hours. After the usual treatment, the *ketone* was obtained as a colourless liquid, b. p. 214—215° (32 g.; 78%) (Found : C, 71·0; H, 5·9. C_9H_9OF requires C, 71·1; H, 5·9%); the *semicarbazone* crystallised from ethanol as leaflets, m. p. 221° (Found : N, 19·8. $C_{10}H_{12}ON_3F$ requires N, 20·1%), and the *oxime* from ethanol as needles, m. p. 79° (Found : C, 64·4; H, 6·1. $C_9H_{10}ONF$ requires C, 64·7; H, 6·0%).

4-*Fluoro*-3-*methylbenzoic Acid*.—4-Fluoro-3-methylacetophenone (10 g.) was oxidised with ice-cold aqueous sodium hypobromite [made from bromine (22 c.c.) and sodium hydroxide (42 g.)]; the resultant *acid* crystallised from benzene as colourless leaflets, m. p. 168—169° (Found : C, 62·2; H, 4·8. $C_8H_7O_2F$ requires C, 62·3; H, 4·5%); 4-*fluoro*-3-*methylbenzoyl chloride* (2·8 g.), prepared from the acid (4 g.) and thionyl chloride (3·5 g.), was a colourless liquid, b. p. 110—115°/20 mm. (Found : C, 55·2; H, 3·4. C_8H_6OClF requires C, 55·5; H, 3·5%).

4-*Fluoro*-3-*methylaniline*.—A cooled solution of 4-fluoro-3-methylacetophenone oxime (2 g.) in anhydrous ether was treated with finely powdered phosphorus pentachloride (2·1 g.) with shaking; after 5 minutes, the mixture was poured on ice, the ethereal layer collected, washed with aqueous sodium carbonate, dried (Na_2SO_4), and freed from solvent, and the solid residue recrystallised from ether–light petroleum; 4-*fluoro*-3-*methylacetanilide* (1·8 g.) formed colourless leaflets, m. p. 74° (Found : C, 64·6; H, 6·1. $C_9H_{10}ONF$ requires C, 64·7; H, 6·0%). 4-Fluoro-3-methylaniline hydrochloride was prepared by heating this amide for 2 hours with hydrochloric acid; the solid hydrochloride obtained gave on basification 4-*fluoro*-3-*methylaniline*, crystallising from light petroleum as prisms, m. p. 35° (Found : C, 67·0; H, 6·3. C_7H_8NF requires C, 67·2; H, 6·4%); it was best characterised by its condensation product with 2 : 3-dichloro-1 : 4-naphthaquinone : 2-*chloro*-3-(4-*fluoro*-3-*methylanilino*)-1 : 4-*naphthaquinone* crystallised from ethanol as red leaflets, m. p. 216° (Found : C, 64·5; H, 3·8. $C_{17}H_{11}O_2NClF$ requires C, 64·7; H, 3·5%).

N-(4-*Fluoro*-3-*methylphenyl*)-β-*naphthylamine*.—The *amine* crystallised from methanol as colourless leaflets (90% yield), m. p. 83° (Found : N, 5·5. $C_{17}H_{14}NF$ requires N, 5·6%).

7-*Fluoro*-5 : 8-*dimethyl*-3 : 4-*benzacridine*.—This *benzacridine* formed from ethanol pale yellow needles, m. p. 175°, b. p. 290—292°/18 mm. (Found : C, 82·6; H, 5·0. $C_{19}H_{14}NF$ requires C, 82·9; H, 5·1%); its *picrate* crystallised from xylene as deep yellow needles, m. p. 250° (decomp. above 210°) (Found : N, 11·3. $C_{25}H_{17}N_4O_7F$ requires N, 11·6%).

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